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RESEARCH ARTICLE

CUTANEOUS NECROSIS INDUCED BY ENOXAPARIN IN OLD FEMALE WITH PROSTHETIC MITRAL VALVE REPLACEMENT AFTER ELECTIVE CARPAL TUNNEL RELEASE

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Abstract

The LMW heparin (enoxaparin) has been shown to be effective (LMWH) for preventing venous thromboembolism, particularly in orthopedic surgery that associated mainly with restriction of mobility. This article reviews detailed history, examination and investigations of a 76-year-old female patient who underwent to elective Carpal Tunnel Syndrome release and complained of rare life-threatening necrotizing skin lesion at the site of Enoxaparin injection, without concomitant Heparin-induced thrombocytopenia.

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Introduction:-

Venous thromboembolism (VTE) comprised of deep vein thrombosis (DVT) and pulmonary embolism (PE) are relatively common diseases that associated with significant morbidity and mortality. ^(1,2) DVT is affecting approximately 100 per 100,000 people per year. ⁽²⁾ It is estimated that approximately 25,000 people are affected in the Kingdom of Saudi Arabia (KSA) annually. ⁽³⁾ Low molecular weight heparin (LMWH), such as Enoxaparin is an anticoagulant that has consensus in clinical practice for preventing deep venous thrombosis and pulmonary embolism in surgical patients. ⁽⁴⁾

Aside from bleeding risk of heparin, there are rare cutaneous side effects have been reported in the literature. ⁽⁵⁾ However, heparin-induced skin necrosis is a rare cutaneous side effect that may have location either at the injection site or at distant. ⁽⁶⁾ Researchers indicated that heparin necrosis begins on average 7 days (range 1–17 days) after starting heparin injections and comes with redness, pain and swelling under the skin. ⁽⁷⁾ Usually, the area of necrosis is only about 3 cm in diameter but can be more extensive. ^(6,7)

The exact mechanism for this notable side effect is controversial but frequently occurs along with heparin-induced thrombocytopenia thus will lead to formation of an antibody-heparin-platelet complex and activate the clotting process resulting in clots in small blood vessels of the skin. ⁽⁸⁾ There are different hypotheses that had been conducted in medical research that aimed to justify the causal association between heparin and cutaneous necrosis. One of these hypotheses is the type III hypersensitivity syndrome that stimulate inflammation of the blood vessels (vasculitis), which then affects the blood supply to the surface skin. ⁽⁹⁾ Presence of fat tissue is another hypothesis that attributed the fat cells as a factor that may lead to poor blood circulation and thus results in the heparin persisting in the injection site and causing further damage. ^(8,9)

This is the case report with detailed history, examination of a 76-year-old female patient with focal skin necrosis at sites of enoxaparin injection and bleeding from the surgical site. The present case aims to highlight successful management option when facing this rare and potentially life-threatening clinical problem.

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Report of the case:

A 76-year-old Saudi female patient had scheduled under the day surgery unit for an elective procedure of left carpal tunnel release. She is a known case of hypertension, diastolic heart failure with pulmonary hypertension, and atrial fibrillation. In addition, she has known to have prosthetic mitral valve replacement (MVR) since 18 years and currently she is on oral anticoagulant (Warfarin 4.5mg once daily).

The procedure of left carpal tunnel release was the surgical treatment as she had carpal tunnel syndrome with left hand pain and numbness. Her symptoms were not improved with non-operative measures. Patient went through the preoperative assessment and there was an advice from cardiology department to stop her regular dose of oral Warfarin and gave her instead the therapeutic dose of low-molecular-weight Heparin (Enoxaparin 80mg, subcutaneously and two times per day).

On the day of surgery, the patient had admitted under the day surgery unit and she underwent to Carpal tunnel release of the left wrist under local anesthesia. The procedure passed smoothly, with no complications and the patient had discharged home on the same day of surgery.

First day postoperative, Warfarin (5mg orally once daily) had resumed by cardiologist along with Enoxaparin injection. Late in the evening, the patient presented to the emergency department complaining of pain and oozing from the surgical site with pain and swelling at the injection site of Enoxaparin at the abdominal wall. The patient had reassured by ER staff, she got dressing on her wounds, and then they discharged her home.

The next day (second day postoperative), the patient presented again to the emergency department and she was complaining of progressive pain with swelling of the left hand, wrist, and forearm. On examination, there was diffuse ecchymosis over the hand, wrist, reaching to the proximal forearm with newly appeared papules and hemorrhagic bullae (**Figure 1**), and tense swelling with mild tenderness with passive stretch test. (Impending compartment syndrome). The distal neurovascular exam was intact, and the capillary refill was <5 sec. In addition to that, there were worsening swelling, induration, and hemorrhagic blister at the injection site of Enoxaparin on the abdominal wall (**Figure 2**). The patient was re-admitted again to the hospital as a case of the hand and forearm impending compartment syndrome due to subcutaneous hematoma.

The cardiologist advised to discontinue subcutaneous Enoxaparin and to start an infusion of heparin as per protocol along with oral Warfarin. The dermatologist suspected Enoxaparin-induced skin necrosis and Heparin-induced thrombocytopenia (HIT syndrome).

The patient referred to hematology for investigations about HIT syndrome, and they stated that she had a low probability for HIT syndrome according to 4Ts score clinical assessment. There was an advice from the hematologist to hold Heparin Infusion and replace it with direct anticoagulant therapy (IV Bivalirudin infusion; direct thrombin inhibitors). Therefore, the patient started on IV Bivalirudin infusion along with warfarin 10mg daily in the cardiac care unit (CCU) for close observation and monitoring.

Significantly, there was no reduction in platelets count ($163 \times 10^9/L$ at admission, $151 \times 10^9/L$ during the hospital stay, $176 \times 10^9/L$ at discharge). Biopsy had taken from the skin lesion at the injection site of the abdominal wall, which revealed focal epidermal vacuolation associated with mild edema at dermis with perivascular infiltrate of lymphocytes with neutrophils and few eosinophils, suggestive of vasculitis, favoring drug-induced.

During the hospital stay, swelling of the hand and forearm showed mild improvement, and the ecchymosis and hemorrhagic bullae became dry with and there was intact neurovascular upon the distal examination. The skin lesions at injection sites improved after local wound care and dressing; no surgical intervention was required (**Figure 3**). There was no skin lesion came up elsewhere all over the body after discontinuation of Heparin and Enoxaparin.

The patient had discharged on oral Warfarin therapy. She was under Follow up appointments with the orthopedic clinic after two weeks, and then one month. However, patient got improvement in her swelling and ecchymosis with evidence of healing in abdominal skin lesion.



Figure 1:-Swelling and ecchymosis of the left wrist and forearm with the presence of hemorrhagic blister associated with bleeding from surgical incision.



Figure 2:- Peri-umbilical skin induration with necrosis and hemorrhagic bullae at the injection site of enoxaparin.



Figure 3:- Left hand of the patient after three weeks of discharge with swelling and ecchymosis improvement and healed surgical wound.

Discussion:-

Unfractionated Heparin (UFH) and Low molecular weight heparin (LMWH) are commonly used anticoagulants that have proven to decrease the risk for deep vein thrombosis and pulmonary embolism in most patients particularly orthopedic in whom restricted mobility may be necessary following several surgical procedures.⁽¹⁰⁾

As our patient has prosthetic mitral valve replacement, she underwent bridging therapy for anticoagulant with a therapeutic dose of LMWH (Enoxaparin 80mg SC twice daily). Studies showed that the prophylactic dose of LMWH for patients with mechanical heart valves who undergo surgical procedures found to be safe and feasible with low risk of minor bleeding and thromboembolic events.^(11,12) Another retrospective cohort study published in 2017, recommended prophylactic dose of LMWH (40mg SC once daily); rather than therapeutic dose; for patients undergoing elective invasive procedures, which showed a low risk for thromboembolic events, and cause less bleeding.⁽¹³⁾

Several adverse reactions were reported secondary to the administration of Heparin, such as Heparin-induced thrombocytopenia (HIT syndrome) and Heparin-induced skin necrosis, which are rare potentially life-threatening adverse reactions, with an incidence of 1-10% and 20%, respectively.^(14, 15) They occur more commonly with unfractionated Heparin (UFH) more than LMWH.^(14, 16) Skin necrosis may progress, causes sepsis, and eventually death.^(17,18) Other adverse effects reported include: major bleeding events⁽¹⁵⁾, venous/arterial thrombosis complicated HIT syndrome in 30%, osteoporosis, and anaphylaxis.⁽¹⁹⁾

Heparin-induced thrombocytopenia (HIT) syndrome can be diagnosed clinically with clinical pretest probability assessment (4Ts score). Score <3 indicates low probability, from 4-6 makes it possible, and greater than 6 highly makes it probable for HIT.^(16,20) Furthermore, Physicians may require some laboratory test to confirm the diagnosis such as platelets count, platelets aggregation test (PAT), Heparin-induced platelets activation (HIPA) assay, serotonin release assay (SRA) in addition to immunologic tests like heparin anti-bodies by an ELISA.^(21,22)

The skin lesions appear within 2-15 days after initiation of the therapy, commonly at the injection site, and manifests as erythema and tenderness, which may evolve into blisters formation and plaques of skin necrosis. Rarely, it may appear distant from the injection sites.⁽⁷⁾ A skin biopsy may help to confirm the diagnosis of heparin-induced skin necrosis by the presence of thrombosis in the dermal/epidermal microvascular structures with infiltration of inflammatory cells providing a picture of vasculitis.^(7,8)

It can be concluded that once skin lesion noticed and confirmed to be related to Heparin exposure, Heparin therapy should be discontinued immediately, and –if required- direct thrombin inhibitors or other non-heparin anticoagulants should be started, such as argatroban or danaproid.^(15,17) These skin lesions may persist up to three months, and most frequently healed spontaneously with local dressing.⁽¹⁷⁾ In some reported cases, surgical debridement followed by split-thickness skin graft may be required.⁽¹⁹⁾

On the contrary, skin necrosis has also been reported with the use of oral anticoagulants such as Warfarin (Coumadin), which usually manifest within 3-10 days after initiation of the therapy because of protein C and protein S deficiency, but it has a lower incidence of systemic thrombosis. Nevertheless, it is considered a critical condition, so discontinuation of Warfarin should be the first step in management.^(19,23) In the present case, the diagnosis of Warfarin-induced skin necrosis was excluded as the patient was on long term period of Warfarin therapy (more than 15 years) for prosthetic mitral valve replacement, with no reported complications, and normal laboratory results of serum protein C and protein S.

Because the patient developed the necrotic skin lesion after initiation of Enoxaparin and resolved after discontinuation of this therapy, she was diagnosed with Heparin-induced skin necrosis without HIT syndrome (negative HIT assay and no fall in platelets count) and confirmed by skin biopsy taken from the injection site. The patient also developed bleeding at the surgical site that put her at risk for developing compartment syndrome. However, it was treated with observation and non-operative measures, and no surgical intervention was required.

In Conclusion:-

although the complications related to administration of Heparin and LMWH are relatively rare, orthopedic surgeons should raise the suspicion for Enoxaparin induced skin necrosis and be aware of these potentially life-threatening adverse reactions. Early recognition and prompt management is crucial to prevent the bad consequences.

Ethical consideration:

Patient was informed that data from the case would be submitted for publication, and she gave her consent.

Conflicts of interest:

None.

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